Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of EP547 in Subjects with Cholestatic Pruritus Due to Primary Biliary Cholangitis or Primary Sclerosing Cholangitis

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Primary objective* To assess the efficacy of EP547 compared to placebo on pruritus as assessed by the Worst Itch Numeric Rating Scale (WI-NRS)Secondary* To assess the efficacy of EP547 compared to placebo on the following:* Pruritus-related quality...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON53412

Source
ToetsingOnline

Brief title
EP547 for Subjects with CP or PSC

Condition

- Hepatic and hepatobiliary disorders

Synonym
Cholestatic Pruritus; Cholangitis

Research involving

Human

Sponsors and support

Primary sponsor: Escient Pharmaceuticals, Inc
Source(s) of monetary or material Support: Industry - Escient Pharmaceuticals

Intervention

Keyword: Cholestatic Pruritus, Efficacy, EP547, WI-NRS

Outcome measures

Primary outcome

The primary estimand of the study is to assess the difference in severity of pruritus in subjects with cholestatic pruritus due to PBC or PSC treated with EP547 or placebo, as measured by change in weekly average WI-NRS after 6 weeks of randomized treatment, regardless of treatment discontinuation and use of prohibited and/or rescue medications.

Secondary outcome

na

Study description

Background summary

Patients with cholestatic liver disease, such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), often suffer from chronic itch or pruritus that is experienced by up to 70% to 80% of these patients over the course of their disease (Mittal 2016).
Patients with cholestatic pruritus have difficulty coping with the intense itching and develop associated stress. Pruritus has a clinically meaningful negative effect on patients* quality of life, sleep, fatigue, emotional state, and social relations (Bassari 2015, Ibrahim 2016), and contributes to the development of skin and soft tissue lesions and/or infections (Ozen 2018).

The pathophysiology of cholestatic pruritus is not fully understood and the

itch-causing pruritogen(s) and their cognate receptor(s) have remained largely elusive. Cholestatic pruritus is often nonresponsive to standard pharmacological treatments, including antihistamines, and instead requires physically removing the causative obstruction (such as gallstones), draining the bile, or transplanting the liver to alleviate itch (Bergasa 2014). Because these procedures are often highly effective, the responsible pruritogens are hypothesized to originate from the liver and bile. Numerous candidate pruritogens are present in bile and upregulated in cholestatic patients, including opioids, lysophosphatidic acid, bilirubin, and bile acids. Therapies targeting these mechanisms, such as opioid antagonists, rifampicin, ileal bile acid transporter inhibitors, and bile acid-binding resins like cholestyramine, are frontline therapy for cholestatic pruritus (Bassari 2015, Mittal 2016); however, efficacy is variable and patients are poorly managed with these medications (Bassari 2015, Mittal 2016).

Although a variety of interventions have been explored, the need for improved treatment of cholestatic pruritus remains high. Therefore, development of additional safe and effective, mechanistically based therapeutic options for this condition is essential.

Study objective

Primary objective
* To assess the efficacy of EP547 compared to placebo on pruritus as assessed by the Worst Itch Numeric Rating Scale (WI-NRS)

Secondary
* To assess the efficacy of EP547 compared to placebo on the following:
* Pruritus-related quality of life using the 5-D Itch Scale
* Pruritus severity using the Patient Global Impression of Severity (PGI-S)
* Overall pruritus response to therapy using the Patient Global Impression of Change (PGI-C)
* To assess the safety and tolerability of EP547
* To assess the pharmacokinetics (PK) of EP547

Exploratory
* To assess the effects of EP547 compared to placebo on the following: o Sleep using the Patient-Reported Outcomes Information System (PROMIS) Short Form - Sleep Disturbance
* Fatigue using the Fatigue Impact Scale for Daily Administration (D-FIS)
* Overall quality of life using the 3-Level EuroQol-5D (EQ-5D-3L)
* Pruritus-related biomarkers (bile acids and heme metabolites)

Study design

EP-547-201 is a randomized, double-blind, placebo-controlled study to evaluate

the effects of EP547 on pruritus over 6 weeks in subjects with cholestatic pruritus due to primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC). Where allowed per regulatory/local requirements, subjects will be able to attend study visits at a physical study site as well as remotely (hybrid model) or at a virtual site where all visits will be conducted remotely (decentralized model). For both the hybrid and decentralized models, a home health nurse visit at the subject's home or work and a telemedicine visit with the study site staff (eg, smartphone or computer) will be arranged to conduct procedures for each remote study visit.

The study includes a Screening Period of up to 4 weeks to assess subject eligibility; a 6-week Double-Blind Treatment Period; a 6-week Open-Label Extension Period; and a 2-week Safety Follow-Up Period after administration of the last dose of study drug (EP547 or placebo). Approximately 58 subjects will be randomized to receive either 100 mg doses of EP547 or placebo orally (PO) once daily (QD) in a 1:1 ratio. In the Open-Label Extension Period, all subjects will receive 100 mg doses of EP547.

Screening Period
The Screening Period will consist of 1 study visit (Visit 1). During this period, subjects will undergo assessments to determine study eligibility. Visit 1 (Day-28 to Day -1) may be conducted over more than 1 day but must be completed between Day -28 and Day -1.

Double-Blind Treatment Period
The Double-Blind Treatment Period will consist of 5 study visits (Visits 2, 3, 4, 5, and 6 [Day 1 and Weeks 1, 2, 3, and 6]). During this period, all subjects who meet eligibility requirements will be enrolled into the study and randomized to receive double-blind, PO, QD doses of EP547 or placebo for 6 weeks beginning on Visit 2 (Day 1). Subjects will be randomized to receive either 100 mg doses of EP547 or placebo in a 1:1 ratio. Randomization will be conducted centrally via an Interactive Web Response System (IWRS) and stratified based on type of cholestatic disease (PBC, PSC). Visit 2 (Day 1) will not have a visit window; however, for the decentralized model, enrollment/randomization and the first dose of study drug may be separated by up to 10 additional calendar days to allow for home delivery of study drug. When enrollment/randomization and first dose of study drug are on separate days, the first dose of study drug is considered Day 1. All other visits in the Double-Blind Treatment Period will have a visit window of ±3 days.

Open-Label Extension Period
The Open-Label Extension Period will consist of 2 study visits (Visit 7 [Week 9] and Visit 8 [Week 12]). During this period, all subjects who complete the Double-Blind Treatment Period and are still receiving study drug will receive open-label 100 mg doses of EP547. Visit 7 and Visit 8 will have a visit window of ±3 days.

Safety Follow-Up Period
Any subject who completes the Open-Label Extension Period or discontinues study drug (EP547 or placebo) early will complete a follow-up visit (Visit 9) approximately 2 weeks (±3 days) after the last dose of study drug.

Intervention

For the Double-Blind Treatment Period, tablets containing 25 mg or 75 mg of EP547 or placebo will be taken orally as intact (swallowed whole, not chewed or crushed) tablets, and taken with water. Doses are to be administered daily at approximately the same time of day after a fast of at least 8 hours. For the Open-Label Extension Period, tablets containing 25 mg or 75 mg of EP547 will be supplied. Subjects receiving EP547 will take one 25-mg and one 75-mg EP547 tablet per dose (for a total dose of 100 mg) and subjects receiving placebo will take 2 placebo tablets per dose.

Study burden and risks

There might be side effects of the study drug EP547, fe: allergic Reaction.
Some symptoms of allergic reactions are as follows:
• Rash
• Wheezing and difficulty breathing
• Dizziness and fainting
• Swelling around the mouth, throat, or eyes
• A fast pulse
• Sweating

Burden of the procedures in the study:
Blood draws via injection or IV: some discomfort or pain when blood is drawn. Participants may faint or pass out. There is a risk of infection, bleeding, or bruising at the site where the injection was.

Electro Cardio Gram (ECG): a mild rash or irritation cab develop where the ECG pads are placed. The rash/irritation is generally mild and usually goes away without treatment.

Other:
Extra time spend for the study: filling in of questionnaires, review of personal information.
Physical examinations will be done.
Study tablets to swallow.

It is hoped that the study drug may provide relief of, or lessening of, itch, one of the signs and symptoms that participants may experience as a result of their liver condition.

Participation in the research study may benefit others by helping the researchers gain valuable information on how people respond to the study drug and whether there should be more clinical studies to see if the study drug may help reduce itch in patients with liver disease.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age 18 to 80 years, inclusive
2. Has experienced self-reported daily or near-daily moderate to severe pruritus before Screening
3. Has a mean daily WI-NRS score indicative of moderate to severe pruritus (score >=4) as recorded using a study-issued electronic device or application (app) during Screening (Day -7 through Day -1); data from at least 4 of the 7

days are required to be considered an acceptable profile
4. If currently taking medications to treat the cholestatic disorder (obeticholic acid [OCA]), must be on a stable dose for >12 weeks before Screening and plans to maintain the regimen throughout the study
5. If currently taking a fibrate, must be on a stable dose for >12 weeks before Screening and plans to maintain the regimen throughout the study
6. Either is not treated with or has been on a stable regimen with any medications to treat pruritus for >4 weeks before Screening and plans to maintain the regimen throughout the study
7. If female, must have a negative serum pregnancy test at Screening and be willing to not donate eggs from Screening until the last dose of study drug
8. Must be able to communicate well with the Investigator, understand and comply with the requirements of the study, and understand and provide written consent
9. For subjects with concomitant inflammatory bowel disease (IBD): a. Colonoscopy (if subject has a colon) or other appropriate endoscopic procedure within 18 months of Day 1 confirming no dysplasia or colorectal cancer b. Subjects with Crohn*s disease (CD) must be in remission as defined by a Crohn*s Disease Activity Index (CDAI) <150 at Screening c. Subjects with ulcerative colitis (UC) must have a Partial Mayo Scoring Index score<=3 with no individual sub-score exceeding 1 point at Screening
10. Documented history of PBC that is consistent with the American Association for the Study of Liver Diseases (AASLD) Practice Guidelines (Lindor 2019), defined as having >=2 of the following 3 factors upon diagnosis: a. History of elevated alkaline phosphatase (ALP) levels b. Historic positive antimitochondrial antibody (AMA) or AMA-M2 by immunofluorescence, enzyme linked immunosorbent assay (ELISA), or immunoblot or if AMA is negative, positive for PBC-specific antibodies (anti-GP210 and/or anti-SP100) c. Liver histology at any point in time consistent with PBC
11. If currently taking ursodeoxycholic acid (UDCA), must be treated for >=1 year, and must be on a stable dose of not more than 20 mg/kg/day for >=12 weeks. If not currently taking UDCA, must not be treated with UDCA within 12 weeks before Screening or plan to be treated with UDCA during the study
12. Documented history of PSC based on either cholangiography (ie, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, or percutaneous transhepatic cholangiogram) or if small duct PSC, confirmed by typical histologic evidence of PSC for >=1 year
13. If currently taking UDCA, must be treated for >=1 year, and must be on a stable dose of not more than 23 mg/kg/day for >=12 weeks. If not currently taking UDCA, must not be treated with UDCA within 12 weeks before Screening or plan to be treated with UDCA during the study.

Exclusion criteria

1.Pruritus is attributed mainly to any disease unrelated to PBC or PSC

2.Prior liver transplant or presently listed for transplantation
3.Is receiving ongoing ultraviolet B (UVB) treatment or plasmapheresis or anticipates receiving such treatments during the study
4.Evidence of compensated or decompensated cirrhosis based on ANY of the following: Historical liver biopsy demonstrating cirrhosis b. Liver stiffness as assessed by a FibroScan® score of >=16.9 kPa for subjects with PBC or >=14.4 kPa for subjects with PSC within 6 months of Screening c. History or presence of portal hypertension with complications, including known gastric or esophageal varices, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, history of variceal bleeds, or related therapeutic or prophylactic interventions
5.History of malignancy of any organ system, including but not limited to hepatocellular carcinoma, cholangiocarcinoma, and gall bladder carcinoma, treated or untreated, within the past 5 years (localized squamous cell or basal cell carcinoma of the skin that have been excised or resolved is not exclusionary)
6.Alternate causes of liver diseases such as hepatic sarcoidosis, alcoholic liver disease, histology confirmed autoimmune hepatitis, overlap hepatitis, or nonalcoholic steatohepatitis (NASH), or uncontrolled viral hepatitis as defined in Protocol
7.Presence of documented secondary sclerosing cholangitis (eg, ischemic cholangitis, recurrent pancreatitis, intraductal stone disease, severe bacterial cholangitis, surgical or blunt abdominal trauma, recurrent pyogenic cholangitis, choledocholithiasis, toxic sclerosing cholangitis due to chemical agents, or any other cause of secondary sclerosing cholangitis) on prior clinical investigations
8.Immunoglobulin G4 (IgG4) >4× upper limit of normal (ULN) at Screening or evidence of systemic IgG4-related disease
9.Current evidence of clinically significant high-grade strictures or presence of biliary stent at Screening
10.History of recurrent bacterial cholangitis or recent episode within 3 months before Screening 11.Endoscopic interventions with therapeutic intent such as biliary duct dilation within 3 months before Screening or planned during the study
12.History of significant small bowel resection or short bowel syndrome
13.Presence of a concomitant disease or a history of any medical condition that, in the opinion of the Investigator, could pose undue risk to the subject, impede completion of the study procedures, or would compromise the validity of the study measurements
14.Clinically relevant medical history, physical examination, vital sign, standard 12-lead electrocardiogram (ECG), chemistry, hematology, urinalysis, or coagulation results at Screening beyond what is expected for subjects with a cholestatic disorder that would place the subject at undue risk as deemed by the Investigator
15.Has any of the following laboratory results at Screening: a.Total bilirubin >2.0 mg/dL; total bilirubin >2.0 mg/dL is acceptable for subjects with medically documented Gilbert*s syndrome if direct bilirubin is <0.3 mg/dL

b.Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5× ULN c.ALP >10× ULN d.International normalized ratio (INR) >1.3 e.Platelet count <150,000/µL f.Urine albumin to creatinine ratio >=30 mg/g
16.Estimated glomerular filtration rate <60 mL/min/1.73 m2 as determined by the Chronic Kidney Disease Epidemiology Collaboration equation at Screening
17.History of human immunodeficiency virus (HIV) or positive for HIV infection at Screening 18.Significant history of abuse of drugs, solvents, or moderate alcohol consumption (>=1 serving or unit/day on average for women and >=2 servings or units/day on average for men) in the past 2 years before Screening
19.Has received a prohibited medication within 2 weeks or 5 half-lives of Day 1, whichever is longer, as described in Protocol
20.Participation in any clinical study with an investigational or approved drug/device within 30 days before Screening or is planning to participate in another clinical study with an investigational or approved drug/device while enrolled in this study
21.History of known or suspected hypersensitivity to any component of the study drug
22.Female who is pregnant, nursing, or intends to become pregnant during the study
23.Is directly affiliated with the study at the study site or is an immediate family member (spouse, parent, child, or sibling; biological or legally adopted) of personnel directly affiliated with the study at the study site
24.Is employed by Escient Pharmaceuticals, Inc., (that is an employee, temporary contract worker, or designee responsible for the conduct of the study) or is an immediate family member of an employee of Escient Pharmaceuticals, Inc.
25.Subject in the opinion of the Investigator, not suitable to participate in the study

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-04-2024
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	EP547
Generic name:	na

Ethics review

Approved WMO Date:	14-02-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-03-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-05-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-10-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-01-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	14-02-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-04-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-04-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-06-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-002526-25-NL
ClinicalTrials.gov	NCT05525520
CCMO	NL82950.018.22